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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JACKSON WALKER LLP
901 MAIN STREET
SUITE 6000
DALLAS, TX 75202

EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,896	RABINOVSKY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008 and 27 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,21-24,26,28,29,31,33,38 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,21-24,26,28,29,31,33,38 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed on 8/11/08 has been entered. Applicants' Response, filed 3/27/08 has been entered. Claims 18-20, 27, 30 are cancelled; claims 17, 21, 24, 41, 43 and 44 are amended; claims 17, 21-24, 26, 28, 29, 31, 33, 38, 41-44 are pending and under current examination.

Applicants filed no substantive remarks with the Response filed 8/11/08, therefore, the Examiner responds to Applicants' remarks, filed 3/27/08.

Election/Restrictions

Applicant's election of claims 17-38 (group II), SEQ ID NO:1 and stimulating angiogenesis as the goal of the claimed treatment method in the response on 2/2/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112 –Enablement

The prior rejection of claims 17-24, 26-31, 33, 38, and 41-44 under 35 U.S.C. 112, first paragraph, for enablement, is withdrawn in view of Applicants' amendment to the claims which removes language directed to fragments of IGF-I.

Written description

The prior rejection of claims 17-18, 24, 27-31, 33, 38, and 41, 42, 44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims which removes language directed to fragments of IGF-I and functional biological equivalents thereof.

Claim Rejections - 35 USC § 112

The prior rejection of claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of Applicants' amendment to the claim which now recites that the promoter *comprises* SEQ ID NO: 3.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, 41-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new ground of rejection, necessitated by Applicants' amendment to the claims.

Claim 17 recites the limitation "or functional biological equivalent thereof" in the third to last line of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 21-24, 26, 28, 29, 31, 33, 38, 41-44 depend from claim 17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 21, 31, 33, 38 and 42 stand rejected under 35 U.S.C. 102(b) as being anticipated by Alila *et al.* (cited previously).

Applicants' Arguments. Applicants argue that the claimed invention is directed to a method of stimulating angiogenesis in a subject who has a muscle injury, and that this is not disclosed in the Alila reference. Applicants argue that Alila do not disclose each and every element of the claims. Applicants argue that the Alila reference at p. 1794, 1st col., last ¶ teaches that gene therapy using formulated plasmids may have potential utility in the treatment of local myoneuropathies, and that one of ordinary skill in the art would have understood this passage to suggest that further experimentation would be required to determine if one of many growth factors could have utility in treatment of local myoneuropathies. Such suggestions fail to place the claimed invention in possession of one of ordinary skill, and such, Applicants argue, Alila does not anticipate the claimed invention. See p. 7 of the Response.

Response to Arguments. These arguments are not persuasive. Alila teach that using their method, one could treat local myoneuropathies (see p. 1794, 1st col, last ¶). This passage clearly relates to the entire paragraph found on p. 1794, 1st col. last¶; namely that the data presented in Alila indicate that a single intramusclar injection of hIGF-I plasmid complexed with PVP produces a localized expression of biologically active hIGF-I. It is clear from this citation of Alila that one of skill in the art would recognize that the methods taught by Alila would necessarily relate to the treatment of myoneuropathies by increasing hIGF-I, as taught in the last sentence of Alila. Accordingly, the Examiner maintains that Alila anticipates the claimed invention because they teach each and every element of the claims.

Alila *et al.* teach the construction of a plasmid (pIG0552), which contains the 5' portion of the chicken skeletal α-actin gene enhancer/promoter, which is operably linked to the human IGF-I cDNA, and flanked by the 3' portion of human growth hormone UTR (see page 1786, 1st col., 1st ¶ and Figure 1). They teach the purified plasmid was formulated with a complex with PVP (polyvinylpyrrolidone) and then

intramuscularly injected into the hind limb of rats (see p. 1787, 1st col., Animal Injections). The muscle samples were then harvested and frozen at various time points and analyzed for hIGF-I expression. Alila *et al.* teach that hIGF-I expression was found localized in the injected muscles (see p. 1790, col. 1-2, bridging ¶).

Accordingly, Alila *et al.* teach the claimed invention, because they teach intramuscular injection of a construct with a myogenic promoter (chicken skeletal α-actin), which is operably linked to a nucleic acid sequence encoding IGF-I, operably linked to a 3'UTR region, and they teach the expression of this plasmid construct localized to muscle tissue. They anticipate claim 42 because Alila teach the human growth hormone 3'UTR .

Alila *et al.* further anticipate specific embodiments of the claims in that they teach delivery via a single administration (claim 31); delivery into muscle which are diploid cells (claim 33); and that the subject is an animal (rat) (claim 38).

In the instant case, Alila *et al.* teach the steps of injection of a specific nucleic acid expression construct which fulfills the limitations of the claims; thus, the property of the nucleic acid, when expressed, is that that it stimulates angiogenesis.

Accordingly, Alila *et al.* anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* further in view of van Deutekom *et al.* (Mol. Med. Today, 214-220, May 1998).

Applicants' Arguments. Applicants argue similarly, as above, that the methods of Alila do not suggest the claimed invention because they do not disclose stimulating angiogenesis in a subject who has an injured muscle. Applicants argue that the van Deutekom reference fails to make up for this teaching. Applicants argue there is no inherent disclosure of stimulating angiogenesis in a subject who has a muscle injury with a method that include injecting the muscle tissue of the injured muscle of the subject an isolated nucleic acid expression construct. Applicants argue that the allegation that the property of stimulating angiogenesis is an inherent property of IGF-I still does not amount to the aforementioned method is necessarily present in the disclosure of Alila.

Response to Arguments. These arguments are not persuasive. The Examiner responds that Alila use IGF-I and inject this into muscle tissue. Applicants also use IGF-I to inject into muscle tissue. Thus, it is clear that the claimed and prior art products appear to be identical or substantially identical. A product and its properties cannot be separated. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In

the instant case the property of stimulating angiogenesis is a property of IGF-I. Applicants have not provided evidence or guidance to show that Alila's method would not result in angiogenesis, or conversely, distinguished Applicants' methods from that of the cited art of record. Accordingly, given that Alila uses the same product, and teaches injecting into muscle tissue, it is reasonable to conclude that this same product, IGF-I, would have the same property as Applicants' method of injection of IGF-I into muscle tissue. The prior rejections of record are maintained.

Alila *et al.* are summarized above. They do not specifically teach mixing the isolated nucleic acid expression construct with a transfection facilitating system before delivery (claim 22); or that the transfection facilitating system is a liposome or cationic lipid (claim 23). However, prior to the time of the claimed invention, van Deutekom teach that intramuscular injection of non-viral vectors – such as plasmid DNAs – which are encompassed by the instant claims, are shown to have low transfection efficiency, and that these efficiencies can be improved by using non-targeted liposomes and/or polylysine-condensed plasmid DNA (see p. 215, 1st col., 1st ¶, Non-Viral Vectors).

Accordingly, given the combined teachings of Alila *et al.* and van Deutekom, it would have been obvious for one of ordinary skill in the art to modify the method of Alila *et al.* to mix the isolated nucleic acid expression construct with a transfection-facilitation system, such as utilizing a liposome, as contemplated by van Deutekom, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as van Deutekom discuss the low transfection efficiency in intramuscular gene delivery, and suggest using non-targeted liposomes to improve efficiency.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 17, 24, 28, 29, 41, 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* (cited above) in view of Draghia-Akli (cited previously), Fewell et al (cited previously) and Isner (cited previously). This rejection has been modified to add claims in light of Applicants' amendment to claim dependency.

Applicants provide the same arguments presented above. The Examiner has addressed these arguments previously.

Alila *et al.* is cited above. Alila *et al.* does not teach a myogenic promoter that comprises SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12) (claim 41), nor do they teach a nucleic acid construct comprising an amino acid sequence of SEQ ID NO: 4 (claim 24), or an expression construct that comprises SEQID NO: 1 (claim 26) and does not teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells (claims 28, 29, 43 and 44).

Draghia-Akli teaches a myogenic promoter consisting of the nucleic acid of SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12). Draghia-Akli teaches a plasmid construct comprising the SPc5-12 promoter operably linked to a nucleic acid encoding human growth hormone releasing hormone (GHRH; page 1182, col. 2, paragr. 3). Draghia-Akli teaches intramuscular injection of said plasmid construct into pigs and then electroporating the injected muscle of said pig to more efficiently deliver said plasmid to the muscle cells (page 1180: col. 1, paragr. 4, line 1 to col. 2, line 10). Draghia-Akli teaches that said SPc5-12 promoter is a powerful synthetic muscle promoter that drives high level expression of operably linked heterologous nucleic acids in a muscle-specific manner (page 1180, col. 1, lines 1-2).

Fewell teaches instramuscular injection of plasmid DNA complexed with the charge polypeptide poly-L-glutamate into mice followed by electroporation. Fewell teaches that injection of a plasmid comprising a nucleic acid encoding factor IX and

that injection of a plasmid comprising a nucleic acid encoding erythropoietin as such (i.e. forming a complex comprising said plasmids and poly-L-glutamate prior to injection) resulted in enhanced expression of said plasmids compared to when said plasmids were injected as saline solution (i.e. when said plasmids were not complexed with poly-L-glutamate). Thus, Fewell teaches that intramuscular injection of plasmid DNA complexed with poly-L-glutamate followed by electroporation results in more efficient transfection of the cells within the injected muscle.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the method of Alila *et al.* with a reasonable expectation of success by: 1) interchanging the avian skeletal chicken skeletal α-actin promoter with the strong muscle-specific synthetic SPc5-12 promoter taught by Draghia-Akli, 2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell and 3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to modify the method of Coleman as such because: 1) Draghia-Akli teaches that the synthetic SPc5-12 promoter drives high level, muscle-specific expression of operably linked nucleic acids, 2) Fewell teaches that complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection and prior to electroporation results in enhanced uptake of said plasmid DNA and 3) both Draghia-Akli and Fewell teach that electroporating muscle after intramuscular injection of plasmid DNA results in enhanced uptake of said plasmid DNA. Increased cellular uptake of plasmid DNA and increased expression of operably linked nucleic acids contained within said plasmid would be advantageous when practicing methods of gene therapy. Thus, the claimed invention as a whole was *prima facie* obvious.

Further, it is noted that pAV2001 (i.e. SEQ ID NO:1 of the instant application) is a hybrid plasmid consisting of fragments of the plasmids taught by Alila (citing Coleman) and Draghia-Akli. The specification on page 42, lines 16-19 recites, "An Nco/HindIII fragment of a SIS II plasmid (Coleman et al., 1995), containing the IGF-I cDNA and the skeletal alpha actin 3'UTR, was cloned into the NcoI/KpnI sites of pSP-HV-GHRH (Draghia-Akli et al., 1999) to generate pSP-IGF-I-SK3'UTR (pAV2001 – SEQID No.: 1)." Thus, an artisan of ordinary skill at the time of the invention would have realized with a reasonable expectation of success that the teachings of Coleman and Draghia-Akli could be combined to generate the plasmid DNA consisting of the nucleic acid sequence of SEQ ID NO:1.

Although neither Alila, Draghia-Akli or Fewell specifically state that IGF-I is an angiogenic factor, Isner teaches a method for stimulating angiogenesis in an ischemic muscle tissue in a human host comprising injecting into said tissue a DNA sequence encoding an angiogenic protein, wherein said DNA sequence comprises a promoter sequence, wherein the angiogenic protein is selected from a group of angiogenic proteins including insulin-like growth factor (IGF-I; claims 1 and 16; col. 4, lines 8-10, 23).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to utilize the methods of Alila, to intramuscularly inject a construct that comprises the construct as taught by Alila, Coleman and Draghia-Akli, and to modify this technique by electroporating the muscle after injection of the plasmid DNA, by methods taught by Fewell, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these modifications, as shown above, that Draghia-Akli teach a strong, muscle-specific promoter, and that complexing plasmid DNA with poly-L glutamate prior to intramuscular injection and electroporation after injection results in more efficient transfection of the cells within the injected muscle. The teachings of Isner provide additional motivation for an artisan of ordinary skill to use a nucleic acid encoding

IGF-I to stimulate angiogenesis in muscle and further support that the claimed invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632